Emerging options for the management of travelers' diarrhea

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Target Audience

This activity has been designed to meet the educational needs of gastroenterologists and nurses involved in the management of patients with travelers' diarrhea.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the epidemiology and morbidity associated with travelers' diarrhea
- Employ recommendations provided in current guidelines on the treatment of mild, moderate, or severe travelers' diarrhea
- Explain the limitations of fluoroquinolones in the management of travelers' diarrhea
- Analyze the results of clinical studies evaluating the activity of emerging therapies for travelers' diarrhea

Faculty

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Robert Steffen, MD—Compensation as the global principal investigator in the phase 3 study sponsored by Dr Falk Pharma comparing rifamycin to ciprofloxacin, which has been summarized in this review. Current or recent consultancy agreements with Aries, Clasado, and Host Therabiomics. Reimbursement from various vaccine producers for lectures.

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Emerging Options for the Management of Travelers' Diarrhea

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Abstract: The incidence of travelers' diarrhea (TD) has slightly decreased due to improvements in the hygienic conditions seen in many destination countries. However, high-risk areas are still widespread. Previous classification based severity on the number of unformed stools passed in 24 hours. Now, TD is differentiated as mild, intermediate, and severe, with the new definitions focusing on the functional impact. Incapacitation is frequent and can result in the need to change travel plans, including cancellation of flights, which results in considerable expense. Guidelines published in 2017 offer detailed recommendations for the prophylaxis and management of TD. For mild TD, antibiotics are no longer recommended. However, antibiotics provide the most rapid symptom relief for patients with intermediate or severe TD, particularly when used in combination with antimotility agents. Fluoroquinolones are no longer the first-line antimicrobials against TD because of widespread resistance and evidence for the increased risk of multidrug-resistant organisms. Also, side effects are of concern. In November 2018, the US Food and Drug Administration approved a new, virtually nonabsorbed antibiotic, rifamycin, for the treatment of TD, based on data showing efficacy without evidence of an increase in multidrug resistance.

Introduction

Travelers' diarrhea (TD) is the most frequent health problem abroad.[1] TD refers to watery or soft stools that are accompanied by symptoms such as fecal urgency, abdominal cramps, nausea, vomiting, or fever. Each year, approximately 15 to 20 million people develop TD.[2] Previous definitions have based severity on the number of unformed stools passed in 24 hours.[3]

Now, TD is differentiated as mild, intermediate, and severe, depending on the degree of incapacitation; the new definitions focus on the functional impact.[3] A mild manifestation of TD is tolerable, is not distressing, and does not interfere with planned activities. An intermediate episode is distressing and interferes with the patient's plans and ability to function, regardless of the number of stools. The patient often has substantial accompanying symptoms. Severe TD leaves the patient completely incapacitated and unable to take part in planned activities. In general, the patient must remain close to a toilet. The presence of fever or gross blood mixed in the stool can indicate dysentery,[2] an invasive disease resulting from damage to the intestinal mucosa. Dysentery is always considered to be severe TD. The distinction between intermediate and severe TD has limited relevance; any degree of incapacitation can be troublesome. For example, if a patient must miss a business meeting, an excursion to an important tourist site, or a flight due to TD, then the episode is incapacitating, regardless of the number of unformed stools or accompanying symptoms.

Without treatment, the average episode of TD lasts approximately 4 days.[2,4,5] In approximately half of

Table 1. Factors Associated With Increased Risk of Acquiring Travelers' Diarrhea

Factors	Mechanism	Predictable Pathogens
Adventure travel, visiting friends and relatives	Varying exposure to contaminated food and beverages	All that cause travelers' diarrhea[4]
Younger age	Unknown; possibly more pathogens ingested (crawling infants, larger appetite in adolescents)	All that cause travelers' diarrhea[4]
Lack of caution in beverage and food selection	Varying exposure to contaminated food and beverages	All that cause travelers' diarrhea[4]
Use of proton pump inhibitor therapy	Altered killing of enteric pathogens from gastric hydrochloric acid	All bacterial, some parasitic (studies only in nontravelers)[61]
	Interleukin 8 AA: high producers leading to greater intestinal inflammation	SNP increases frequency of enteroaggregative *Escherichia coli* and *Clostridium difficile*[62,63]
	Lactoferrin: high producers leading to greater intestinal inflammation	SNP increases frequency of all that cause travelers' diarrhea and travelers' diarrhea with intestinal inflammation[64]
	High producers of interleukin 10 are more susceptible to travelers' diarrhea, which may reflect immunomodulatory effects of heat-labile toxin of enterotoxigenic *E coli,* stimulating increases in interleukin 10	SNP increases frequency of enterotoxigenic *E coli* travelers' diarrhea[65]
Certain genetic factors (mostly polymorphism associations)	Osteoprotegerin: immunoregulatory member of tumor necrosis factor receptor superfamily that may function as an anti-inflammatory modulator that increases susceptibility to travelers' diarrhea	Especially inflammatory forms of all that cause travelers' diarrhea[66]
	CD14: receptor for bacterial lipopolysaccharide binding associated with the innate immune response to enteric infection and inflammation; different SNPs may increase susceptibility to travelers' diarrhea; others may lead to protection	SNPs leading to high production are associated with travelers' diarrhea[67]
	Type O blood may influence enteric infection through uncertain mechanisms	Cholera and severe cholera caused by *Vibrio cholerae* O1[68]
	Not possessing the nonsense mutation in the *FUT2* gene that provides resistance to infection related to virus attachment and internalization	Noroviruses[69]

SNP, single-nucleotide polymorphism.

Data from Steffen R et al. *JAMA*. 2015;313(1):71-80.[9]

patients, symptoms resolve within 48 hours. Some people experience a spontaneous cure after a few hours, but in other cases, TD can persist for 2 weeks or even longer, particularly in patients with an underlying disease.[6]

Epidemiology

The incidence of TD has slightly decreased due to improvements in the hygienic conditions seen in many destination countries in the past decades.[7] During the period just after World War II, even southern Europe had a fairly high incidence of TD. The incidence has drastically decreased in this area,[8] as well as in countries in which average income rose from low or even intermediate levels. For example, the incidence rates of TD have decreased in China and other countries in East Asia, and also in large parts of South America.[7] In these areas, the incidence rates are at an intermediate level, which means that 8% to 20% of visitors will develop TD during the first 2 weeks of their stay. Destinations with high incidence rates, in which more than 20% of visitors will develop TD, include large portions of Central America, as well as countries in South Asia, such as India, Pakistan, Bangladesh, and Nepal. Other high-risk destinations include some areas in the Middle East and nearly all of Africa (with the exception of South Africa). Tourist resorts, even in these areas, are increasingly taking great care to reduce the risk of TD among their guests, with some success.

Risk Factors

Risk factors for TD are related to the environment and the host (Table 1).[9] Environmental risk factors include the macro-epidemiology, meaning a specific country or region, as well as the micro-epidemiology, such as hotels.

Table 2. Risk of Travelers' Diarrhea in a New Destination Among People Who Traveled in the Previous 12 Months

		Total[a]	With TD	Without TD	*P* Value
		n (%)	n (%)	n (%)	
Previous antibiotic use	No	133 (77.8)	49 (36.8)	84 (63.2)	0.309
	Yes	38 (22.2)	17 (44.7)	21 (55.3)	
History of TD	No	158 (92.4)	60 (38.0)	98 (62.0)	0.376
	Yes	13 (7.6)	7 (53.8)	6 (46.2)	
TD risk at previous destination[b]	No/low	80 (46.8)	34 (42.5)	46 (57.5)	0.362
	Intermediate	53 (31.0)	21 (39.6)	32 (60.4)	
	High	38 (22.2)	11 (28.9)	27 (71.1)	
Same region	No	142 (86.1)	51 (36.2)	90 (63.8)	
	Yes	23 (13.9)	9 (39.1)	14 (60.9)	

TD, travelers' diarrhea.

[a]There was missing information for some of the variables.

[b]No/low: <8% (including participants who have not travelled within the past 12 months); intermediate: 8% to 20%; high: >20% (according to Steffen R et al. *JAMA*. 2015;313(1):71-80[9]).

Data from Kuenzli E et al. *J Travel Med*. 2017;24(5).[26]

According to a survey on the incidence of TD at hotels in Jamaica with at least 40 clients,[10] one hotel had zero cases, a few had an incidence of less than 10%, and some exceeded 30%. The incidence of TD mirrors the hygienic conditions in the kitchen.[11] TD can affect anyone, even guests at 5-star hotels.[2]

Other environmental risk factors include the characteristics of travel. Backpackers who obtain raw or improperly cooked food from street vendors are at highest risk.[7,12-14] Trips that involve multiple destinations have a higher incidence rate as compared with a visit to one location. The incidence of TD has been shown to be higher in all-inclusive trips, most likely because visitors may overindulge in unlimited alcoholic drinks.[14,15] Consumption of alcohol can result in diarrhea, even without contamination from food and beverages. Mountaineering is also associated with a considerable risk of TD. Higher rates have been seen among travelers to the Mount Everest region in Nepal and Denali (formerly known as Mount McKinley) in Alaska.[7,16-18]

There are several host risk factors. In all studies, the incidence of TD is highest among young people, ages 15 to 30 years.[19-21] The reason is unknown, but it may be because younger people have a larger appetite and therefore ingest more pathogens as compared with senior travelers.[9,22] This age-related difference is maintained even among groups of travelers who stay at the same hotel with all-inclusive menus. TD is not more frequent in either sex, although women may have a stronger perception of the disorder and seek care more often.[23] Travelers originating in countries with an intermediate or high risk of TD have a far lower incidence rate compared with those from low-risk countries.[1,24,25] Also, those who stay in a developing country apparently develop some immunity, which partially protects them for a few months during subsequent travel (Table 2).[26] There may be a genetic predisposition toward developing the disorder.[9] Preexisting illnesses, such as gastrointestinal disorders and possibly immunodeficiency, may result in a high risk of TD. Lack of gastric acids has also been associated with a high risk.[27]

Complications and Impact

In the acute phase of TD, the foremost complication is dehydration. Patients may collapse, particularly when in a tropical climate.

Incapacitation is frequent and can be troubling. For example, if several family members or friends are traveling together, even if only one of them develops TD, it can be disruptive for the entire group. One or more of the healthy travelers may need to stay behind to care for the person with TD. Cancellation of flights and other travel arrangements can result in considerable expense.

Longer-Term Complications

Intermediate or long-term complications include irritable bowel syndrome,[7,28] as well as acquisition of extended-spectrum beta lactamase-producing Enterobacteriaceae.[29] More rare complications include reactive arthritis, hemolytic-uremic syndrome, Guillain-Barré syndrome, and diarrhea associated with *Clostridium difficile*.[7,30]

Etiology of TD

TD can be caused by bacteria, viruses, and parasites (Table 3).[3] Bacteria are responsible for at least 80% of cases, whereas viruses cause approximately 5% to 10%. These statistics vary

Table 3. Estimated Regional Differences in the Etiology of Travelers' Diarrhea[a]

Organism	Reported Pathogens (%)			
	Latin America and Caribbean	Africa	South Asia	Southeast Asia
Enterotoxigenic *Escherichia coli*	≥35	25-35	15-25	5-15
Enteroaggregative *E coli*	25-35	<5	15-25	No data
Campylobacter	<5	<5	15-25	25-35
Salmonella	<5	5-15	<5	5-15
Shigella	5-15	5-15	5-15	<5
Norovirus	15-25	15-25	5-15	<5
Rotavirus	15-25	5-15	5-15	<5
Giardia	<5	<5	5-15	5-15

[a]Studies do not uniformly report on all pathogens; no pathogen was identified in up to 50% of cases.

Data from Steffen R et al. *JAMA*. 2015;313(1):71-80,[9] based on studies conducted in 2002 to 2011.[70-75]

according to geographic location. Up to 60% of infections have a mixed etiology.

Parasites, such as *Entamoeba histolytica*, *Giardia lamblia*, or *Cryptosporidium*, are a rare cause of TD,[31] accounting for less than 5%, or even less than 2%, of cases, depending on the destination. However, TD caused by parasites tends to persist after the patient returns home. In industrialized countries, the percentage of patients with TD caused by a pathogen is far higher than 5% because these cases tend to last longer and require treatment. Most cases caused by bacteria or a virus will eventually resolve without treatment.[32]

Prevention

Dietary Methods

The traditional rule for prevention of TD was, "Boil it, cook it, peel it, or forget it." There is, however, no evidence that this approach substantially reduces the rates of TD.[33] There may even be higher rates of diarrhea among travelers who tried to be careful about what they ate, as compared with those who claimed to eat anything, including salads from buffets or even beef tartar and raw oysters.[4,15] These studies, however, have often been biased by a retrospective approach. There has been only one prospective study, which was performed at my clinic.[34] Unfortunately, the answer rate in this study was too low to permit any conclusions. It is therefore not known whether so-called dangerous foods should be avoided. Only a small proportion of travelers follow the advice to eat food that is boiled, cooked, or peeled.[34] Most travelers drink fruit juices, eat salads, and consume food from buffets; often, there is nothing else available.[15]

Medical Prophylaxis

Drug prophylaxis for TD is more often recommended and used in the United States than elsewhere. In fact, European travelers are even reluctant to use prophylaxis against malaria. Bismuth subsalicylate is an option for any traveler for the prevention of TD.[3] Antibiotic prophylaxis is prescribed in certain circumstances, such as patients with a preexisting illness of the gastrointestinal tract or those likely to develop serious complications after TD.[3] Antimicrobial prophylaxis might also be considered for patients attending important functions, who cannot risk being incapacitated for even a few hours. Rifaximin is the recommended antibiotic for use as prophylaxis.[3] Fluoroquinolones are no longer recommended.

Treatment

The treatment options for TD vary according to the severity of the case. Oral rehydration therapy as a supportive measure is the treatment of choice for infants, children, and the elderly. It is necessary to avoid dehydration and electrolyte imbalance. Such medications are available everywhere. In contrast, there are advantages to equipping future travelers with a travel kit with additional TD medication, since in many countries TD patients otherwise are at risk of counterfeit drugs,[35] obsolete medication, or even unnecessary hospitalization by some doctors practicing close to tourist resorts.[36]

Mild

According to 2017 guidelines from Riddle and colleagues, mild TD should not be treated with antibiotics.[3] A mild episode can be treated with small doses of antimotility agents, such as loperamide, or bismuth subsalicylate. (In Europe, bismuth subsalicylate is not widely available and rarely used.) Activated charcoal and dimenhydrinate are not recommended for TD patients.

Moderate

In some cases, antibiotics can be used to treat patients with moderate TD.[3] Antibiotics, particularly when used in combination with antimotility agents, provide the most rapid symptom relief for patients with TD. Alone, they can reduce the average duration to slightly longer than a day, or even half a day when combined with loperamide.[3] Single-dose antibiotic regimens are preferred. Options mainly include azithromycin and rifaximin. The recently approved rifamycin is also an option for moderate TD.[37]

Until a few years ago, fluoroquinolones were the most commonly used class of antibiotics. There is increasing reluctance to use fluoroquinolones because of increasing resistance, acquisition of multiresistant pathogens, and risk of adverse events.[3,38,39] There is evidence for the increased risk of multidrug-resistant organisms, particularly

with ciprofloxacin. The recent guidelines cite an incrementally increasing association between travel, TD, and use of antibiotics with the acquisition of multidrug-resistant bacteria.[3] Before they leave for a trip, patients should be informed about how this risk can be balanced against the benefits associated with the use of antibiotics.

Another concern with traditional antibiotics is their side effects. Ciprofloxacin in particular has been associated with adverse events.[40,41]

Caution should be exercised when using rifaximin as empirical therapy for moderate diarrhea in regions associated with a high risk of invasive pathogens.

Loperamide can be used as monotherapy or adjunctive treatment for moderate TD.[3] Bismuth subsalicylate is another option.

Severe

Patients with severe TD should receive treatment with antibiotics, possibly combined with loperamide.[3] Single-dose regimens may be used. Azithromycin is the preferred antibiotic. Fluoroquinolones or nonabsorbable rifaximin may be used to treat severe, nondysenteric TD. Similar to the treatment of moderate TD, the recently approved rifamycin is an option for the treatment of severe TD.[37]

Currently, the most commonly used antibiotics for TD are azithromycin and nonabsorbable rifaximin. Both of these treatments are recommended by the new guidelines.[3] A disadvantage to azithromycin is that it may cause nausea, particularly if used at a higher dosage. Rifaximin and rifamycin are nonabsorbable and therefore do not cause any such side effects. In patients with dysentery, azithromycin is the first choice because rifaximin and rifamycin are unlikely to be effective in an invasive infection.[3]

Rifamycin

The new MMX formulation of rifamycin (Aemcolo, Aries Pharmaceuticals, Inc. [a Cosmo Pharmaceuticals N.V. Company]) was approved for TD by the US Food and Drug Administration in November 2018.[42] Rifamycin is similar to rifaximin, an enteric antibiotic that is poorly absorbed.[43,44] Rifamycin incorporates a multimatrix (MMX) technology, which delays release of the drug after ingestion.[45] The drug is released when it encounters intestinal pH levels of 7 or higher.[46] Rifamycin is therefore active only in the colon and the lower part of the ileum. Similarly to rifaximin, as a nonabsorbable antibiotic, rifamycin is associated with a low rate of adverse events.[46] This therapy also has anti-inflammatory properties.[47]

Study Data

An in vitro study by Farrell and colleagues showed that rifamycin was potent against enteropathogens commonly associated with TD.[48] Rifamycin was tested for activity against 911 enteropathogens and 30 *C difficile* isolates gathered from global surveillance studies. Values of minimum inhibitory concentration (MIC) were measured. Against Enterobacteriaceae strains, MIC_{50} values ranged from 32 µg/mL to 128 µg/mL for all but 1 strain (an enterotoxigenic *Escherichia coli* at >512 µg/mL). Against non-Enterobacteriaceae strains, MIC_{50} values ranged from 2 µg/mL to 8 µg/mL. (The one exception was *Campylobacter* species, which had MIC values >512 µg/mL.)

Rifamycin was very active (MIC_{50}, ≤0.03 µg/mL) against 26 of 30 strains of *C difficile* (including 1 hypervirulent NAP1 strain). Among the 4 remaining strains (which also included a hypervirulent NAP1 strain), MIC values ranged from 256 µg/mL to 512 µg/mL. Less activity against *C difficile* strains (including a hypervirulent NAP1 strain) was observed with rifaximin (MIC_{50}, 0.12 µg/mL), metronidazole (MIC_{50}, 0.25 µg/mL), and vancomycin (MIC_{50}, 0.5 µg/mL).

In a study of healthy volunteers, rifamycin was poorly absorbed after oral treatment given in single- and multiple-dose regimens.[46] The oral bioavailability was 0.1%. The amount of systemically absorbed drug excreted in the urine was less than 0.01% of the administered dose (in both the single- and multiple-dose regimens). In the feces, the administered dose was eliminated at a rate of 87%. The absolute bioavailability was 0.0410 ±0.0617 after a single intravenous injection and after a single oral dose under fasting conditions (as calculated by the mean percent ratio between total urinary excretion amounts).

A phase 2 trial of rifamycin vs rifaximin confirmed the efficacy and safety of the new treatment among 115 patients with active infectious diarrhea.[49] Treatment was successful in 47.8% of the rifamycin arm vs 50.9% of the rifaximin arm. The median time to last unformed stool (TLUS) was 67.5 hours with rifamycin vs 65.5 hours with rifaximin. Isolates of *Campylobacter jejuni*, *C lari*, *E coli*, *Anaerobiospirillum*, *Salmonella enteritidis*, and *Shigella flexneri* identified at baseline were no longer retrievable after treatment with rifamycin.

Adverse events occurred in 29 patients treated with rifamycin vs 25 patients treated with rifaximin (Table 4). There were similar rates of constipation, worsening of diarrhea/aggravated diarrhea, and development of yeasts in feces.

A randomized, double-blind phase 3 trial by DuPont and colleagues compared rifamycin (2 × 200 mg twice daily for 3 days) vs placebo.[50] The primary endpoint was TLUS, defined as the interval between the first dose of study drug and the time the last unformed stool was passed. TLUS was 46.0 hours with rifamycin vs 68.0 hours with placebo, a significant difference (P=.0008). A clinical cure was reported in 81.4% of the rifamycin arm vs 56.9% of the placebo arm (Figure 1). The rates of pathogen eradication were 67.0% with rifamycin vs 54.8% with placebo, but this difference did not reach statistical significance (P=.0836). After treatment with rifamycin, in vitro studies showed resistance to rifamycin in some remaining bacteria,

Table 4. Summary of Some Adverse Events That Occurred Throughout a Study of Rifamycin vs Rifaximin (Safety Population)

Adverse Event	Rifamycin	Rifaximin
Headache	14	12
Nausea	3	1
Constipation	4	4
Aggravated diarrhea	3	4
Diarrhea	1	—
Pyrexia	1	1
Dehydration	1	1
Abdominal wind	1	1
Abdominal cramps	1	1
Abdominal pain	1	2
Abdominal spasm	—	1

Data from Di Stefano AFD et al. *Antiinfect Agents*. 2013;11:192-203.[49]

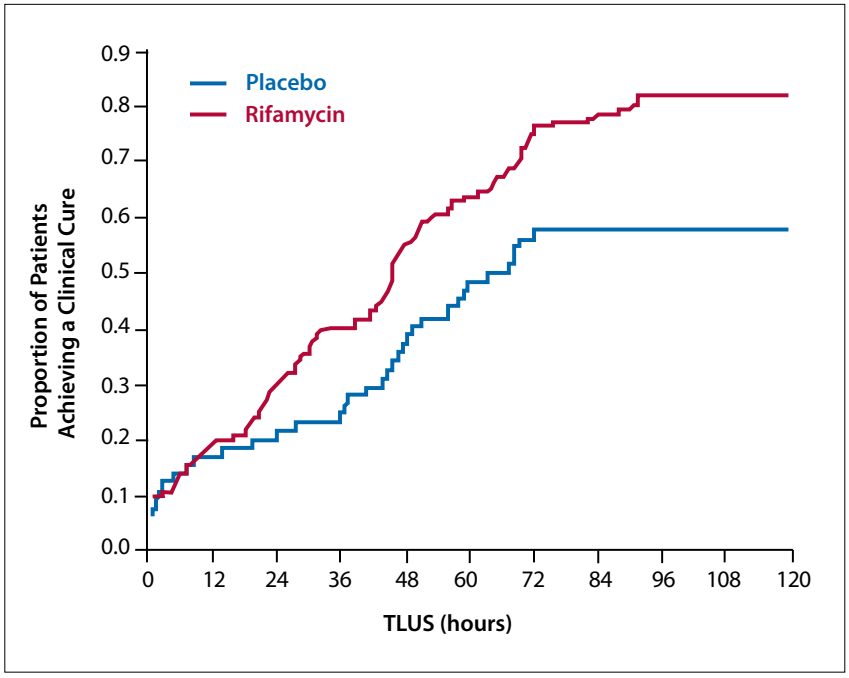

Figure 1. Rates of clinical cure in a phase 3 trial comparing rifamycin vs placebo. TLUS, time to last unformed stool. Adapted from DuPont HL et al. *J Travel Med*. 2014;21(6):369-376.[50]

but this finding did not correspond to lower efficacy.

Adverse events occurred in 29.6% of the rifamycin arm vs 38.5% of the placebo arm. Diarrhea, the most common adverse event, was reported in 10.0% of the rifamycin patients and 16.9% of the placebo patients. In the rifamycin arm, the next most common adverse events were headache (occurring in 8.5%) and constipation (occurring in 3.5%). There were no reports of amebic dysentery or gastrointestinal infection among patients treated with rifamycin. Each of these adverse events occurred in 3.1% of patients receiving placebo.

My colleagues and I performed a randomized, double-blind phase 3 study comparing rifamycin (400 mg twice daily) vs ciprofloxacin (500 mg twice daily; at the time of study design, the first-line drug) for the treatment of TD.[51] The study was designed to prove noninferiority of rifamycin compared with ciprofloxacin. The primary endpoint was TLUS, which was defined as the interval between the first dose of the study drug and the last unformed stool passed before the end of the clinical cure period. This conservative definition of TLUS differs from that seen in other trials, which limits the duration to before the start of the clinical cure period.

The study randomly assigned treatment to 835 international visitors who developed acute TD. Most patients were traveling in India (n=805), and the others were in Guatemala or Ecuador (n=30). Patients had experienced at least 3 unformed, watery or soft stools within 24 hours before randomization, with the illness lasting no more than 72 hours. All patients also reported at least 1 moderate to severe sign or symptom of enteric infection (eg, gas/flatulence, nausea, vomiting, abdominal cramps or pain, rectal tenesmus, fecal urgency). Exclusion criteria included passage of gross bloody stools, known or suspected infection with a nonbacterial pathogen (eg, human immunodeficiency virus or viral hepatitis), moderate or severe dehydration, history of inflammatory bowel disease or celiac disease, and use of more than 2 doses of an antidiarrheal medication within 24 hours or use of an antibiotic within 7 days prior to randomization.

Treatment was completed by 814 patients (97.5%) in the study, and discontinuation rates were similar in both arms. In the per-protocol analysis, the median TLUS was 42.8 hours with rifamycin vs 36.8 hours with ciprofloxacin. This difference indicated that rifamycin was noninferior to ciprofloxacin (P=.0035). The intent-to-treat analysis confirmed this noninferiority. The median TLUS

was 44.3 hours with rifamycin vs 40.3 hours with ciprofloxacin (*P*=.0011). There were no statistically significant differences between the treatment groups for the secondary endpoints of clinical cure rate, treatment failure rate, and requirement of rescue therapy. A subgroup analysis found that earlier initiation of either treatment corresponded to a shorter TLUS.

Adverse events occurred in 14.8% of the rifamycin arm and 14.9% of the ciprofloxacin arm. Adverse drug reactions occurred in 8.1% vs 7.5%, respectively. There were no reports of serious adverse events or deaths.

As mentioned, multidrug resistance is a concern with ciprofloxacin and other fluoroquinolones. An interesting finding in the trial was that rifamycin did not increase multidrug resistance.[51] Among patients in the ciprofloxacin arm, colonization rates with extended-spectrum beta lactamase–producing *E coli* increased by 6.9% after 3 days of treatment (Figure 2). In contrast, this rate did not increase among patients treated with rifamycin. These data were shown in a study presented at the 2017 Digestive Disease Week and the 15th Conference of the International Society of Travel Medicine.[52,53]

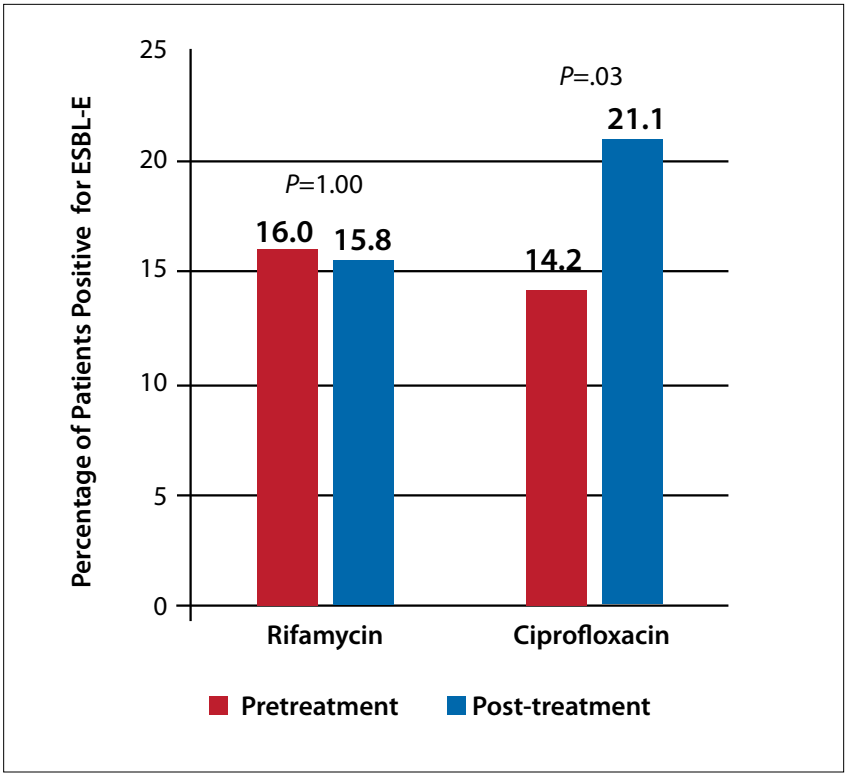

Figure 2. Colonization rates with ESBL-E in a phase 3 trial of rifamycin vs ciprofloxacin. ESBL-E, extended-spectrum beta lactamase–producing *E coli*. Adapted from Steffen R et al. *J Travel Med*. doi: org/10.1093/jtm/tay116.[51]

Other Emerging Treatments

Studies of the gut microbiome in travelers with and without diarrhea may clarify the use of current and novel preventive, diagnostic, and therapeutic approaches.[54] Currently, there is insufficient evidence to recommend the use of commercially available prebiotics or probiotics to prevent or treat TD.[3,55,56] However, there is reason to expect that next-generation probiotics could bolster colonization resistance against pathogens and thus prevent TD.[57] Since there is a lack of evidence supporting the use of antisecretory agents, such as crofelemer and racecadotril, in the setting of TD, these agents are not broadly recommended.[3] Only zaldaride has been evaluated, but this agent is not marketed anywhere.[58]

Currently, there is no effective vaccine against TD. In Canada, the oral cholera vaccine originally was recommended as prophylaxis against TD, but since 2015, the indication has been limited to TD associated with *E coli*. In the European Union, this vaccine is used only to protect against cholera, and most experts agree that it has, at best, a minimal impact on the TD incidence rate[59]—far less, for example, than the influenza vaccine. Several vaccine candidates are in the pipeline.[60]

Evaluation of a Patient After a Trip

When a patient returns with TD after a trip, it is first necessary to take a history and to assess the symptoms, particularly the degree of incapacitation. The date of onset is important, to determine whether the diarrhea is acute, persistent, or chronic. Also, one needs to learn what therapy already has failed to improve the condition. Some patients may have received obsolete or inappropriate therapies during their travels.[36] For the management, it is not necessary to learn where the patient was traveling, what he or she ate, or whether the trip was for business or pleasure, but it is always nice to express a general interest and empathy for the patient's history. The patient may urgently require rehydration and/or treatment for relief of symptoms. In general, patients should not be treated with the same medication they already received.

Traditional microbiologic testing is not needed in uncomplicated cases; hopefully, the patient will be cured before the results arrive. In contrast, testing is recommended in patients with severe TD or persistent symptoms or when antibiotic therapy was unsuccessful.[3] In patients with dysentery, there is general agreement that laboratory tests are needed. Molecular testing for clinically relevant pathogens is preferred when rapid results are needed

or when nonmolecular tests did not establish a diagnosis. If the patient previously received antimicrobial agents without any improvement of the condition, then I would obtain a stool test for parasites. If the patient has received an antimicrobial agent and is very incapacitated or even has dysentery, then I may consider another antibiotic. Despite the lack of evidence, I occasionally may use probiotics when the symptoms are mild and my intention is to avoid harm while gaining time toward a spontaneous cure.

Approximately 6% of patients have diarrhea that is persistent (lasting more than 2 weeks).[6] This type of TD may be associated with undiagnosed parasitic gastrointestinal infection, which needs to be treated appropriately. The probability of a bacterial infection decreases with the duration of symptoms. In some cases, the episode of TD unmasks a previously undiagnosed gastrointestinal disease, such as idiopathic inflammatory bowel disease, celiac sprue, or lactose intolerance. Initial evaluation should include a complete blood count to check for anemia and eosinophilia, stool analysis (polymerase chain reaction is preferred), an assay for *C difficile*, and celiac serologies. Patients may exhibit postinfectious sequela of an enteric infection.

Conclusion

Management of TD continues to evolve. Guidelines offer detailed recommendations for the many different scenarios that can arise. For the many patients with mild TD, antibiotics are now contraindicated since they may be associated with adverse events and resistance. In contrast, these agents may or should be used in more severe forms of TD. While quinolones have lost their position as first-choice antimicrobials in TD for a number of reasons, the nonabsorbed agents rifaximin and the newer treatment rifamycin are attractive options for the therapy of noninvasive TD. In particular, it has been shown that patients receiving rifamycin for the treatment of TD are not at increased risk of acquiring multidrug-resistant pathogens.

Disclosure

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